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㉔ Substituted azetidinones, pharmaceutical compositions containing them, and their use for the manufacture of anti-inflammatory and antidegenerative medicaments.

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㉕ Proprietor: MERCK & CO. INC., 126, East Lincoln Avenue P.O. Box 2000, Rahway New Jersey 07065-0900(US)

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㉖ Inventor: Shrenik, K. Shah, 25 Denise Court, Metuchen New Jersey 08840(US)

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㉗ Inventor: Firestone, Raymond A., 60 Hunter Avenue, Fanwood New Jersey 07023(US)

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㉘ Inventor: Barker, Peter L., 518 Hort Street, Westfield New Jersey 07090(US)

㉗ References cited:

㉙ Inventor: Hagmann, William, 309 Hyslip Avenue, Westfield New Jersey 07090(US)

EP-A-0 042 026

㉚ Inventor: Doherty, James B., 559 Columbia Street, New Milford New Jersey 07646(US)

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㉛ Inventor: Dom, Conrad P., 972 Fernwood Avenue, Plainfield New Jersey 07062(US)

AT-B-295 547

㉜ Representative: Ahner, Francis et al, CABINET REGIMBEAU, 26, avenue Kléber, F-75116 Paris(FR)

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DE-A-1 945 542

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Description**BACKGROUND OF THE INVENTION**

5 We have found that a group of new substituted azetidinones are potent elastase inhibitors and therefore are useful anti-inflammatory/antidegenerative agents.

10 Proteases from granulocytes and macrophages have been reported to be responsible for the chronic tissue destruction mechanisms associated with inflammation, including rheumatoid arthritis and emphysema. Accordingly, specific and selective inhibitors of these proteases are candidates for potent anti-inflammatory agents useful in the treatment of inflammatory conditions resulting in connective tissue destruction, e.g. rheumatoid arthritis, emphysema, bronchial inflammation, osteoarthritis, spondylitis, lupus, psoriasis, atherosclerosis, sepsis, septicemia, shock, periodontitis, cystic fibrosis and acute respiratory distress syndrome.

15 The role of proteases from granulocytes, leukocytes or macrophages are related to a rapid series of events which occurs during the progression of an inflammatory condition:

20 (1) There is a rapid production of prostaglandins (PG) and related compounds synthesized from arachidonic acid. This PG synthesis has been shown to be inhibited by aspirin-related nonsteroidal anti-inflammatory agents including indomethacin and phenylbutazone. There is some evidence that protease inhibitors prevent PG production;

25 (2) There is also a change in vascular permeability which causes a leakage of fluid into the inflamed site and the resulting edema is generally used as a marker for measuring the degree of inflammation. This process has been found to be induced by the proteolytic or peptide cleaving activity of proteases, especially those contained in the granulocyte, and thereby can be inhibited by various synthetic protease inhibitors, for example, N-acyl benzisothiazolones and the respective 1,1-dioxides. Morris Zimmerman et al., *J. Biol. Chem.*, 255, 9848 (1980); and

30 (3) There is an appearance and/or presence of lymphoid cells, especially macrophages and polymorphonuclear leukocytes (PMN). It has been known that a variety of proteases are released from the macrophages and PMN, further indicating that the proteases do play an important role in inflammation.

35 In general, proteases are an important family of enzymes within peptide bond cleaving enzymes whose members are essential to a variety of normal biological activities, such as digestion, formation and dissolution of blood clots, the formation of active forms of hormones, the immune reaction to foreign cells and organisms, etc., and in pathological conditions such as the degradation of structural proteins at the articular cartilage/pannus junction in rheumatoid arthritis etc.

40 Elastase is one of the proteases. It is an enzyme capable of hydrolyzing the connective tissue component elastin, a property not contained by the bulk of the proteases present in mammals. It acts on a protein's nonterminal bonds which are adjacent to an aliphatic amino acid. Neutrophil elastase is of particular interest because it has the broadest spectrum of activity against natural connective tissue substrates. In particular, the elastase of the granulocyte is important because, as described above, granulocytes participate in acute inflammation and in acute exacerbation of chronic forms of inflammation which characterize many clinically important inflammatory diseases.

45 Proteases may be inactivated by inhibitors which block the active site of the enzyme by binding tightly thereto. Naturally occurring protease inhibitors form part of the control or defense mechanisms that are crucial to the well-being of an organism. Without these control mechanisms, the proteases would destroy any protein within reach. The naturally occurring enzyme inhibitors have been shown to have appropriate configurations which allow them to bind tightly to the enzyme. This configuration is part of the reason that inhibitors bind to the enzyme so tightly (see Stroud, "A Family of Protein-Cutting Proteins" *Sci. Am.* July 1974, pp. 74-88). For example, one of the natural inhibitors, α_1 -Antitrypsin, is a glycoprotein contained in human serum that has a wide inhibitory spectrum covering, among other enzymes, elastase both from the pancreas and the PMN. This inhibitor is hydrolyzed by the proteases to form a stable acyl enzyme in which the active site is no longer available. Marked reduction in serum α_1 -antitrypsin, either genetic or due to oxidants, has been associated with pulmonary emphysema which is a disease characterized by a progressive loss of lung elasticity and resulting respiratory difficulty. It has been reported that this loss of lung elasticity is caused by the progressive, uncontrolled proteolysis or destruction of the structure of lung tissue by proteases such as elastase released from leukocytes J. C. Powers, *TLBS*, 211 (1976).

55 Rheumatoid arthritis is characterized by a progressive destruction of articular cartilage both on the free surface bordering the joint space and at the erosion front built up by synovial tissue toward the cartilage. This destruction process, in turn, is attributed to the protein-cutting enzyme elastase which is a neutral protease present in human granulocytes. This conclusion has been supported by the following observations:

60 (1) Recent histochemical investigations showed the accumulation of granulocytes at the cartilage/pannus junction in rheumatoid arthritis; and

(2) a recent investigation of mechanical behavior of cartilage in response to attack by purified elastase demonstrated the direct participation of granulocyte enzymes, especially elastase, in rheumatoid cartilage destruction. H. Menninger et al., in Biological Functions of Proteinases, H. Holzer and H. Tschesche, eds. Springer-Verlag, Berlin, Heidelberg, New York, pp. 196-206, 1979.

5

Accordingly, an object of this invention is to discover new protease inhibitors, especially elastase inhibitors, useful for controlling tissue damage and various inflammatory or degenerative conditions mediated by proteases particularly elastase.

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Another object of the present invention is to provide pharmaceutical compositions for administering the active substituted azetidinones as protease inhibitors especially human leukocyte elastase.

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Still a further object of this invention is to provide a method of controlling inflammatory conditions by administering a sufficient amount of one or more of the active, substituted azetidinones in a mammalian species in need of such treatment.

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15 DETAILED DESCRIPTION OF THE INVENTION

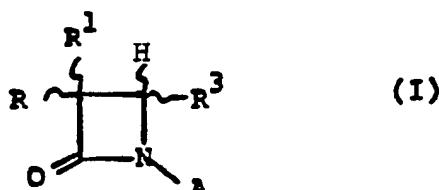
This invention relates to potent elastase inhibitors of formula (I) which are useful in the prevention, control and treatment of inflammatory/degenerative conditions especially arthritis and emphysema.

25

A large number of derivatives of the azetidinone of formula (I) are known antibiotics which have been described in patents DE 2 911 589, DE 2 824 554, 2 748 827, US 4 493 389 and various publications.

The formula of the substituted azetidinones which are found to exhibit anti-inflammatory and anti-degenerative activities by the present invention are represented as follows:

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wherein:

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— the wavy lines mean that R, R₁, H and R₃ can be at the α or the β positions and

— R is: H or

C₁₋₆ alkyl.

— R₁ is: H

C₁₋₆ alkyl

C₂₋₆ alkenyl

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C₁₋₆ alkoxy or
C₆H₅

— R₃ is: SO-C₁₋₆ alkyl

COO-C₁₋₆ alkyl

COO-CH₂-C₆H₅ with C₆H₅ eventually substituted in para-position by -COOH

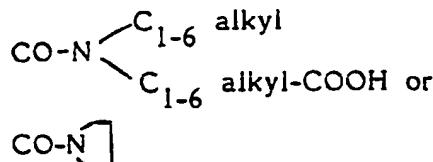
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O-CO-C₁₋₆ alkyl with C₁₋₆ alkyl eventually substituted in terminal position by -COOH

O-CO-C₆H₅

O-C₆H₅ with C₆H₅ eventually substituted in para-position by -COOH

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with the proviso that when A = H, if R = R₁ = H, R₃ is different of -O-CO-C₁₋₆ alkyl, -O-CO-C₆H₅ or -O-C₆H₅ and if R = R₁ = CH₃, R₃ is different from O-CO-CH₃.

— A is: H

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CO-C₁₋₆ alkyl, C₁₋₆ alkyl eventually substituted by -COOH in terminal position

CO-C₆H₅

CO-NH-C₁₋₆ alkyl

CO-O-C₁₋₆ alkyl

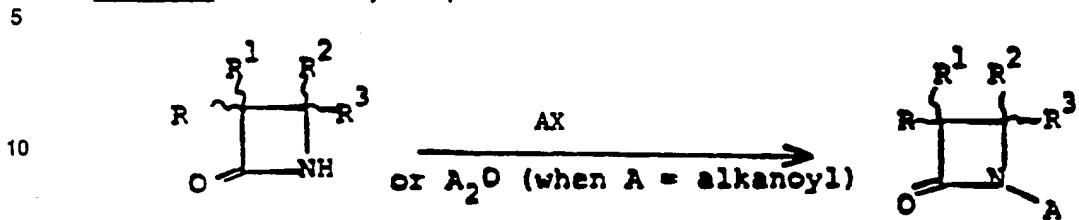
SO₃⁻(Bu)₄N⁺, or

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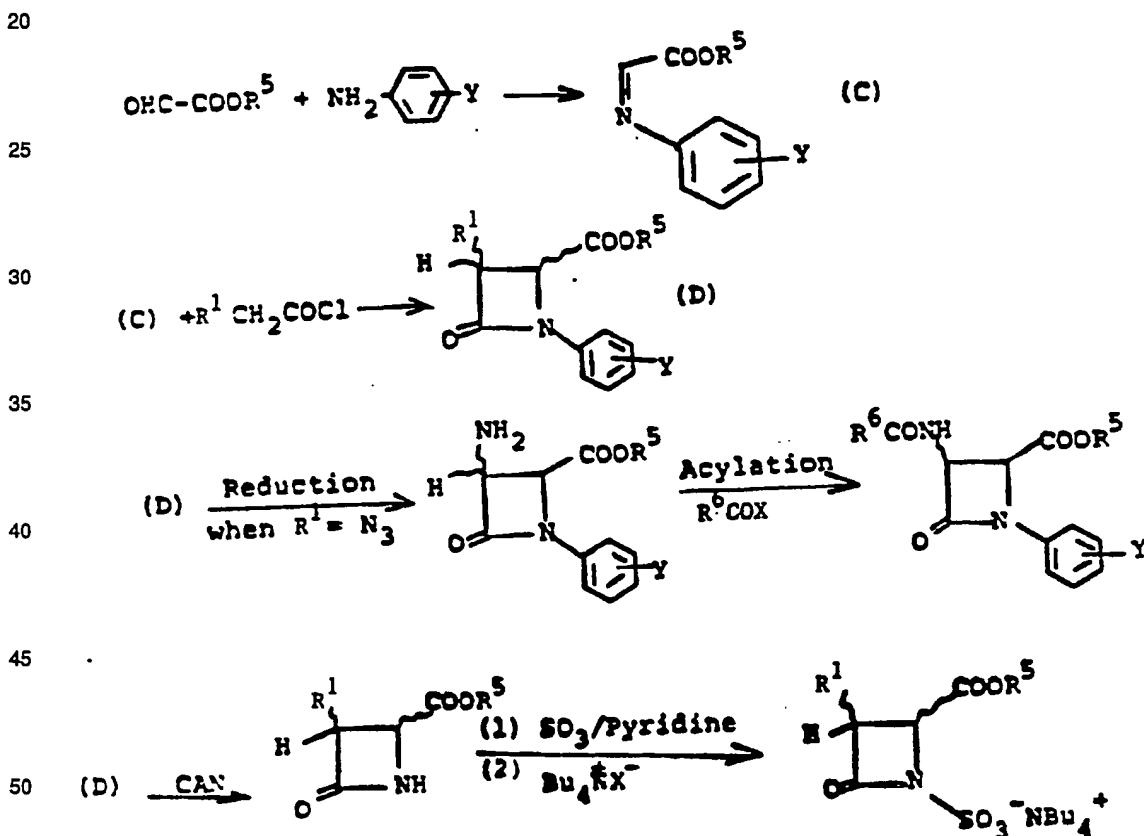
SO₂-C₆H₅, C₆H₅ being substituted in para-position by NO₂ or CH₃.

The compounds of the present invention may be obtained from derivatives which are ever disclosed in litterature (AT 375 640, AT 295 547, DE 3 007 298, DE 2 842 466, DE 2 046 823, DE 2 046 822, DE 1 945 542, GB 2 093 839, GB 1 604 752, US 4 510 086, EP 0 076 621, EP 0 042 026).

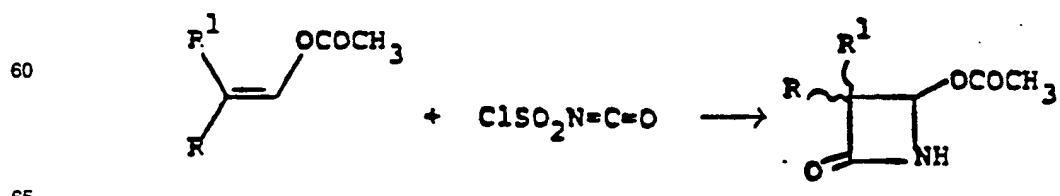
Scheme (a) as illustrated by Examples 1-4.



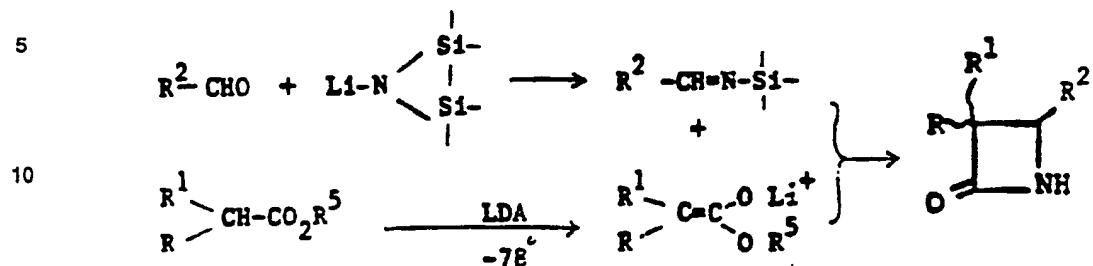
Scheme (b) as illustrated by Examples 5-7.



Scheme (c) as illustrated by Examples 2-3.

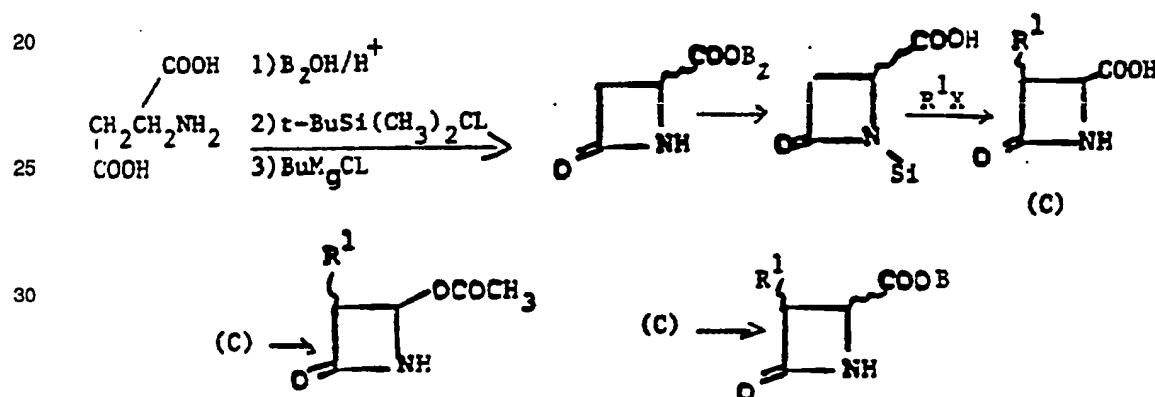


Scheme (d) as taught by Hart, D.J. *et al.*, (J. Org. Chem., **48**, pp. 289-294, 1983); the following class of compounds can be prepared.



15 wherein B₅ is H, C₁₋₆ alkyl or aryl.

Scheme (e) as taught by P.J. Reider and E.J.J. Grabowski (*Tet. Lett.*, **23**, p. 2293, 1982); the following groups of compounds can be prepared.



wherein R¹ is as previously defined and B is alkyl or benzyl.

This invention also relates to a method of treating inflammation in patients using a compound of Formula (I), particularly an especially preferred compound as the active constituent.

40 It has been found that the compounds of Formula (I) have anti-inflammatory and/or anti-degeneration activity and are effective in the prevention and inhibition of edema and granuloma tissue formation as shown below in Table I by the effective inhibition of the proteolytic function of human granulocyte elastase.

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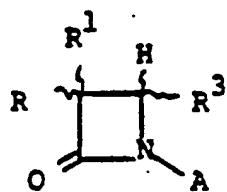
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TABLE I



	R	R¹	R³	A	IC ₅₀ (μg/ml)
15					
	H	H	SOCH ₃	COCH ₃	10
20	H	H	OCOCH ₃	COCH ₃	3
	H	C ₂ H ₅	OCOCH ₃	H	15
	H	C ₂ H ₅	OCOCH ₃	COCH ₃	0.1
25	H	n-propyl	OCOCH ₃	COCH ₃	0.01
	H	C ₆ H ₅ (trans)	COOC ₂ H ₅	H	10
	H	H	COOCH ₂ C ₆ H ₅	SO ₂ (p-C ₆ H ₅ -NO ₂)	3
30	CH ₃	CH ₃	OCOCH ₃	COCH ₃	0.5
	H	C ₆ H ₅ (trans)	COOC ₂ H ₅	SO ₂ (p-C ₆ H ₅ -NO ₂)	4
35	H	C ₆ H ₅ (cis)	COOC ₂ H ₅	SO ₂ (p-C ₆ H ₅ -NO ₂)	3
				2	
40	H	n-C ₃ H ₅ -	OCOCH ₃	- + SO ₃ (Bu) ₄ N	8
	H	CH ₂ -CH-(cis)	COOC ₂ H ₅	SO ₂ (p-C ₆ H ₄ NO ₂)	0.02
	H	C ₂ H ₅ -(cis)	COOC ₂ H ₅	SO ₂ (p-C ₆ H ₄ NO ₂)	0.05
45	H	C ₂ H ₅ -(trans)	COOC ₂ H ₅	SO ₂ (p-C ₆ H ₄ NO ₂)	0.01
	H	C ₂ H ₅ -(trans)	COOC ₂ H ₅	SO ₂ (p-C ₆ H ₄ CH ₃)	0.01
	H	n-C ₃ H ₅ -(cis)	COOC ₂ H ₅	SO ₂ (p-C ₆ H ₄ NO ₂)	0.06
50	H	CH ₃ CH ₂ -CH-(cis)	COOC ₂ H ₅	SO ₂ (p-C ₆ H ₄ NO ₂)	0.05

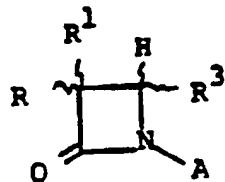
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TABLE II

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R	R ¹	R ³	A	IC ₅₀ (μg/ml)	K _i (μM)	k ₂ /K _i (M ⁻¹ Sec ⁻¹)
H	H	SOCH ₃	COCH ₃	10.00		
H	H	OCOCH ₃	COCH ₃	3.00		
H	C ₂ H ₅	OCOCH ₃	H	15.00		
H	C ₂ H ₅	OCOCH ₃	COCH ₃	0.10	0.36	15100
H	n-propyl	OCOCH ₃	COCH ₃	0.01		
H	C ₆ H ₅ (trans)	COOC ₂ H ₅	H	10.00		
H	H	COOCH ₂ C ₆ H ₅	SO ₂ (p-C ₆ H ₅ -NO ₂)	3.00		
CH ₃	CH ₃	OCOCH ₃	COCH ₃	0.50		
H	C ₆ H ₅ (trans)	COOC ₂ H ₅	SO ₂ (p-C ₆ H ₅ -NO ₂)	4.00		
H	C ₆ H ₅ (cis)	COOC ₂ H ₅	SO ₂ (p-C ₆ H ₅ -NO ₂)	3.00		
H	CH ₃ O	COOCH ₂ C ₆ H ₅	COCH ₃	2.00		
H	n-propyl	OCOCH ₃	SO ₃ ⁻ (Bu) ₄ ⁺	8.00		
H	C ₂ H ₃ (cis)	COOC ₂ H ₅	SO ₂ (p-C ₆ H ₅ -NO ₂)	0.02		
H	C ₂ H ₅ (cis)	COOC ₂ H ₅	SO ₂ (p-C ₆ H ₅ -NO ₂)	0.05	3925	
H	C ₂ H ₅ (trans)	COOC ₂ H ₅	SO ₂ (p-C ₆ H ₅ -NO ₂)	0.05	39300	
H	C ₂ H ₅ (trans)	COOC ₂ H ₅	SO ₂ (p-C ₆ H ₅ -CH ₃)	0.01		
H	n-propyl (trans)	COOC ₂ H ₅	SO ₂ (p-C ₆ H ₅ -NO ₂)	0.06		
H	CH ₃ CHCH (cis)	COOC ₂ H ₅	SO ₂ (p-C ₆ H ₅ -NO ₂)	0.05		
H	C ₂ H ₅	OCOCH ₂ CH ₂ COOH	COCH ₃	2.00	4514	
H	C ₂ H ₅ (trans)	OCOPh	COCH ₃	0.19	81000	

TABLE II (Continued)

5	R	R ¹	R ³	A	IC ₅₀ (μ g/ml)	Ki (μ M)	k ₂ /Ki (M ⁻¹ sec ⁻¹)
	H	C ₂ H ₅ (cis)	OCOPh	COCH ₃		0.21	28500
10	H	C ₂ H ₅	OCOCH ₃	COCH ₂ CH ₂ COOH		1.43	2250
	H	C ₂ H ₅ (cis)	OCOCH ₃	COPh		0.14	
	H	C ₂ H ₅ (trans)	OCOCH ₃	COPh		0.34	76600
15	H	C ₂ H ₅ (trans)	OPh	COCH ₃		4.30	5270
	H	C ₂ H ₅ (trans)	OC ₂ H ₅	COCH ₃		11.90	1670
20	H	C ₂ H ₅ (trans)	OPh-p-COOH	COCH ₃		3.40	8727
	H	C ₂ H ₅ (trans)	OPh-p-COOH	COOC ₂ H ₅		2.10	8680
	H	C ₂ H ₅ (trans)	OPh-p-COOH	CONHCH ₃		16.50	
25	H	C ₂ H ₅ (cis)	CON(CH ₂) ₄	SO ₂ (p-C ₆ H ₅ -CH ₃)		27.70	541
	H	C ₂ H ₅ (cis)	COOCH ₂ C ₆ H ₅ -p-COOH	SO ₂ (p-C ₆ H ₅ -CH ₃)		4.20	299
	H	C ₂ H ₅ (cis)	CON(CH ₃)CH ₂ COOH	SO ₂ (p-C ₆ H ₅ -CH ₃)		22.00	165

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IC₅₀ is the effective dosage in micrograms per milliliter (μ g/ml) for 50% inhibition of the enzyme activity two minutes after time zero. Ki is the concentration of the inhibitor (micromolar, μ M) giving 50% of the control enzyme activity. k₂/Ki (M⁻¹ sec⁻¹) is the second order rate constant of inactivation of the enzyme.

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Protocol – Enzyme Assays for the Inhibition of Human Polymorphonuclear Leukocyte Elastase Via Hydrolysis of N-t-Boc-alanyl-alanyl-prolylalanine-p-nitroanilide Reagents:

45 0.05M TES (N-tris[hydroxymethyl]methyl-2-amino-ethanesulfonic acid) Buffer, pH 7.5.
0.2 mM N-t-Boc-alanyl-alanyl-prolyl-alanine-p-nitroanilide (Boc-AAPAN).

To prepare substrate, the solid (m.w. 550) was first dissolved in 10.0 ml DMSO. Buffer at pH 7.5 was then added to a final volume of 100 ml.

Crude extract of human polymorphonuclear leukocytes (PMN) containing elastase activity.
50 Inhibitors (azetidinones) to be tested dissolved in DMSO just before use.

Assay Procedure:

55 To 1.0 ml of 0.2 mM Boc-AAPAN in a cuvette, 0.01–0.1 ml of DMSO with or without inhibitor was added. After mixing, a measurement was taken at 410 m μ to detect any spontaneous hydrolysis due to presence of test compound. 0.05 Milliliters of PMN extract was then added and the Δ OD/min at 410 m μ was measured and recorded. Beckman model 35 spectrophotometer was used.

Results:

60 Results in Table I were reported as IC₅₀, i.e., effective dosage in micrograms per milliliter (μ g/ml) for 50% inhibition of the enzyme activity 2 minutes after zero time.
Alternatively, results in Table II were expressed as Ki, the micromolar concentration of the inhibitor (μ M) giving 50% of the control enzyme activity; or as k₂/Ki which is the second order rate constant in per mole per second for inactivation of the enzyme.

Comments:

The elastase activity in the crude PMN extract may vary from one preparation to another. A control of each new batch is run, and the volume added in the assay is adjusted according to activity.

5 Accordingly, the compounds of Formula (I) can be used to reduce inflammation and relieve pain in diseases such as emphysema, rheumatoid arthritis, osteoarthritis, gout, bronchial inflammation, atherosclerosis, sepsis, septicemia, shock, periodontitis, cystic fibrosis, infectious arthritis, rheumatic fever and the like.

10 For treatment of inflammation, fever or pain, the compounds of Formula (I) may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, dogs, cats, etc., the compounds of the invention are effective in the treatment of humans.

15 The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparation. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or 20 alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

25 30 Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

35 Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate. The said aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or 40 more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

45 50 Oily suspension may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

55 Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

60 The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oils, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

65 Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and

coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

5 The compounds of Formula (I) may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

10 For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the anti-inflammatory agents are employed.

15 Dosage levels of the order to 0.2 mg to 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (10 mg to 7 gms. per patient per day). For example, inflammation is effectively treated and anti-pyretic and analgesic activity manifested by the administration from about 0.5 to 50 mg of the compound per kilogram of body weight per day (25 mg to 3.5 gms per patient per day). Advantageously, from about 2 mg to about 20 mg per kilogram of body weight per daily dosage produces highly effective results (50 mg to 1 gm per patient per day).

20 The amount of active ingredient that may be combined with the carrier materials to produce dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 5 mg to 5 gm of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 25 mg to about 500 mg of active ingredient.

25 It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

EXAMPLE 1

35 1-p-nitrophenylsulfonyl-4-benzyloxycarbonyl azetidin-2-one

30 Diazabicycloundecane (152 mg, 1 mM) was added to a mixture of 205 mg (1 mM) azetidinone and 181 mg (1 mM) p-nitrobenzenesulfonyl chloride in 10 ml methylene chloride at room temperature. After stirring 2-1/2 hours, the orange solution was washed with water, dried over $MgSO_4$, and concentrated in vacuo.
40 The residue was chromatographed on silica gel in hexane/ethyl acetate to yield 64 mg (17%) of 1-p-nitrophenylsulfonyl-4-benzyloxycarbonyl azetidin-2-one.
NMR ($CDCl_3$): δ 3.3 (2H, doublet-quartet), 4.8 (qt. 1H), 5.2 (s, 2H), 7.2 (s, 5H), 8.2 (mlt. 4H).

EXAMPLE 2

45 1-Acetyl-3,3-dimethyl-4-acetoxyazetidin-2-one

Step A: Preparation of 2-methyl-prop-1-enylacetate

50 A mixture of 72 g (1 M) isobutyraldehyde, 153 g (1.5 M) acetic anhydride and 12 g (0.125 M) potassium acetate was refluxed seven hours. The cooled reaction mixture was washed with water and stirred with 300 ml saturated $NaHCO_3$ at 0° for 45 minutes. The organic phase was dried over K_2CO_3 to yield a yellow oil which was distilled at atmospheric pressure to give 35.41 g (31%) of 2-methyl-prop-1-enylacetate, b.p. 122-126°.
55 NMR ($CDCl_3$): δ 1.6 (s, 6H), 2.1 (s, 3H), 6.9 (mlt. 1H).

Step B: Preparation of 3,3-dimethyl-4-acetoxyazetidin-2-one

60 Chlorosulfonyl isocyanate (16 ml) was added to a solution of 22.8 g (0.2 M) 2-methyl-prop-1-enylacetate in 50 ml methylene chloride at 0° under nitrogen. After stirring at 0° for 20 hours, the reaction mixture was added to a mixture of 20 ml water, 90 g ice, 48 g $NaHCO_3$ and 16.6 g Na_2SO_3 and stirred at 0° for 30 minutes. This was then extracted with 300 ml CH_2Cl_2 and the organic phase washed with brine, dried over $MgSO_4$ and concentrated in vacuo to give 27.75 g oil which was chromatographed on silica gel in hexane/ethyl acetate to yield 2.17 g (8.5%) of 3,3-dimethyl-4-acetoxyazetidin-2-one.
65 NMR ($CDCl_3$): δ 1.2 (s, 3H), 1.3 (s, 3H), 2.2 (s, 3H), 5.6 (s, 1H).

Step C: Preparation of 1-acetyl-3,3-dimethyl-4-acetoxyazetidin-2-one

5 A mixture of 283.3 mg (1.8 mM) 3,3-dimethyl-4-acetoxyazetidin-2-one, 2 ml pyridine and 2 ml acetic anhydride was heated to 100° in a sealed tube for 36 hours. The reaction mixture was concentrated *in vacuo* and the residue chromatographed on silica gel in hexane/ethyl acetate to yield 295 mg (82%) of 1-acetyl-3,3-dimethyl-4-acetoxyazetidin-2-one.
 NMR (CDCl₃): δ 1.2 (s, 3H), 2.2 (s, 3H), 2.5 (s, 3H), 6.1 (s, 1H).

EXAMPLE 3

1-Acetyl-4-acetoxy-3-n-propylazetidin-2-oneStep A: Preparation of Pent-1-enylacetate

15 A mixture of 86 g (1M) valeraldehyde, 153 g (1.5 M) acetic anhydride, and 12 g (0.125 M) potassium acetate, was refluxed for 8 hours. The cooled mixture was then stirred with 100 ml saturated aqueous NaHCO₃ for one hour. The organic phase is separated, dried over K₂CO₃, and distilled at 40 mm to yield 46.15 g (45%) of pent-1-enylacetate, b.p. 89°C.
 NMR (CDCl₃): δ 1.0 (tr, 3H), 1.2–2.0 (mlt., 4H), 2.1 (s, 3H), 4.7–5.6 (mlt., 1H), 7.0–7.3 (mlt., 1H).

Step B: Preparation of 4-acetoxy-3-n-propylazetidin-2-one

20 Eight hundred microliters of chlorosulfonyl isocyanate was added to a solution of 1.28 g (10 mM) pent-1-enyl acetate in 5 ml methylene chloride at 0° under nitrogen. After stirring at 0° 5 days, the reaction mixture was added dropwise to a mixture of 5 g ice, 1.15 ml water, 2.82 g NaHCO₃ and 1.0 g Na₂SO₃ and stirred at 0° for 30 minutes. The mixture was extracted with 2 × 25 ml methylene chloride and the combined organic phases washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The residue was chromatographed on silica gel in hexane/ethyl acetate to yield 60 mg *trans* 4-acetoxy-3-n-propylazetidin-2-one (3.4%).
 NMR (CDCl₃): δ 1.0 (mlt., 3H), 1.7 (mlt., 4H), 2.2 (s, 3H), 3.2 (tr, 1H), 5.6 (s, 1H), 6.7 (lrs, 1H).

Step C: Preparation of 1-acetyl-4-acetoxy-3-n-propylazetidin-2-one

25 A mixture of 56 mg (0.33 mM) 4-acetoxy-3-n-propylazetidin-2-one, 1 ml acetic anhydride and 1 ml pyridine was stirred at 100° in a sealed tube for 24 hours. After concentrating *in vacuo* the residue was chromatographed on silica gel in hexane/ethyl acetate, to yield 16 mg (23%) 1-acetyl-4-acetoxy-3-n-propylazetidin-2-one.
 NMR (CDCl₃): δ 1.0 (br tr, 3H), 1.7 (mlt., 4H), 2.2 (s, 3H), 2.4 (s, 3H), 3.2 (tr, 1H), 6.1 (d, 1H).

EXAMPLE 4

1-Acetyl-4-methylsulfinylazetidin-2-oneStep A: Preparation of 1-acetyl-4-methylthioazetidin-2-one

35 A mixture of 300 mg (2.6 mM) 4-methylthioazetidin-2-one, 10 ml acetic anhydride and 10 ml pyridine was stirred at 100° in a sealed tube 24 hours. After concentrating *in vacuo*, the residue was chromatographed on silica gel in hexane/ethyl acetate to yield 324 mg (78%) of 1-acetyl-4-methylthioazetidin-2-one.
 NMR (CDCl₃): δ 2.4 (s, 3H), 2.41 (s, 3H), 3.2 (doublet-quartet, 2H), 5.1 (doublet-doublet, 1H).

Step B: Preparation of N-acetyl-4-methylsulfinylazetidin-2-one

55 A mixture of 130 mg (0.82 mM) N-acetyl-4-methylthioazetidinone and 200 mg (0.93 mM) 80% m-chloroperbenzoic acid in 5 ml methylene chloride was stirred at room temperature 5 minutes. After removing the solvent *in vacuo*. The residue was chromatographed in 2–2000 μ silica gel plates in hexane/ethyl acetate to yield 57 mg (40%) of 1-acetyl-4-methylsulfinylazetidin-2-one.
 NMR (CDCl₃): δ 2.4 (s, 3H), 2.6 (s, 3H), 3.5 (mlt., 2H), 4.9 (mlt., 1H).

EXAMPLE 5

4-Carboethoxy-3-methoxyazetidin-2-one

60 To a solution of 1.4 g of 4-carboethoxy-3-methoxy-1-(p-methoxyphenyl)azetidin-2-one in 50 ml acetonitrile at 0° was added a solution of 8.23 g of ceric ammonium nitrate in 50 ml H₂O over 3 minutes. Af-

ter stirring at 0° for 1 hour the solution was poured into 200 ml of 10% sodium sulfite and extracted with 3 × 75 ml of ethyl acetate. The combined organic extracts were washed with 10% sodium sulfite and saturated sodium chloride solutions and dried over sodium sulfate. Filtration and evaporation gave an amber oil which was recrystallized from methylene chloride/hexane to give 700 mg of 4-carboethoxy-3-methoxyazetidine-2-one; m.p. 91–92°.

5 NMR (CDCl₃): δ 7.1 (br.s, 1H), 4.7 (dd, J₁=2, J₂=5, 1H), 4.3 (d, J=5, 1H), 4.15 (q, J=7, 2H), 3.4 (s, 3H), 1.25 (t, J=7, 3H).

Following substantially the same procedure as described in Example 5 but using an appropriate 3-substituted azetidinone compounds (a)–(c) were prepared:

10 (a) 4-Carboethoxy-3-phenylazetidin-2-one-2-(cis and trans)

15 NMR (CDCl₃): cis: δ 7.2 (s, 5H), 6.4 (br.s, 1H), 4.7 (d, J=6, 1H), 4.4 (d, J=6, 1H), 3.7 (q, J=7, 2H), 0.75 (t, J=7, 3H); trans: δ 7.2 (s, 5H), 6.9 (br.s, 1H), 4.3 (br.d, J=2, 1H), 4.1 (q, J=7, 2H), 4.0 (d, J=2, 1H), 1.2 (J=7, 3H).

(b) 4-Carboethoxy-3-vinylazetidin-2-one(cis and trans)

20 NMR (CDCl₃) cis: δ 7.1 (br.s., 1H), 5.2–5.8 (m, 3H), 4.0–4.4 (m, 4H), 1.25 (t, J=7, 3H); trans: δ 7.25 (br.s., 1H), 5.0–6.2 (m, 3H), 4.1 (q, J=7, 2H), 3.9 (d, J=2, 1H), 3.7. (dd, J₁=2, J₂=7, 1H), 1.2 (t, J=7, 3H).

(c) 4-Carboethoxy-3-ethylazetidin-2-one

25 Cis: NMR (CDCl₃): δ 6.9 (br. s., 1H); 4.2 (m, 3H); 3.4 (dd, J₁=6, J₂=8, 1H); 1.51 (q, J=8, 2H); 1.2 (t, J=7, 3H); 1.0 (t, J=8, 3H).
Trans: NMR (CDCl₃): δ 6.8 (br. s., 1H); 4.2 (q, J=7, 2H); 3.8 (d, J=2, 1H); 3.2 (dd, J₁=2, J₂=7, 1H); 1.8 ((dq, J₁=2, J₂=8, 2H); 1.2 (t, J=7, 3H); 1.0 (t, J=8, 3H).

30 EXAMPLE 6

4-Carboethoxy-3-methoxyazetidin-2-one-1-sulfonic acid tetrabutylammonium salt

To a solution of 4-carboxy-3-methoxyazetidin-2-one in 5 ml of pyridine at 80° was added 250 mg of sulfur trioxide pyridine complex, and the resulting mixture was stirred for 30 minutes at 80°. The solution was poured into 100 ml of 0.5 N KH₂PO₄ and extracted with 2 × 25 ml of methylene chloride. The combined organic washes were back-extracted with 25 ml of KH₂PO₄ solution. The combined aqueous phases were then treated with 680 mg of tetrabutylammonium hydrogen sulfate and extracted with 3 × 50 ml of methylene chloride. After drying (sodium sulfate) and evaporation of the organic phase the crude 4-carboethoxy-3-methoxy azetidin-2-one-1-sulfonic acid tetrabutylammonium salt was chromatographed to yield pure as an oil.

35 NMR (CDCl₃): δ 4.55 (d, J=6, 1H), 4.5 (d, J=6, 1H), 4.1 (q, J=7, 2H), 3.4 (s, 3H), 3.2 (m, 8H), 0.8–1.8 (m, 31H).

40 Applying the same procedure as described above, the following tetrabutylammonium salt of other azetidine derivative was prepared:

45 4-Carboethoxy-3-vinylazetidin-2-one-1-sulfonic acid tetrabutylammonium salt

EXAMPLE 7

4-Carboethoxy-1-(p-nitrobenzenesulfonyl)-3-phenylazetidin-2-one

To a solution of 720 mg of 4-carboethoxy-3-trans-phenylazetidin-2-one in 20 ml methylene chloride at 0° were added sequentially 595 mg of p-nitrobenzenesulfonyl chloride and 0.48 ml of DBU. The solution was stirred for several hours, diluted with 50 ml of methylene chloride, washed once with water and dried over sodium sulfate. Filtration and evaporation gave a crude residue which was chromatographed to yield pure 4-carboethoxy-1-(p-nitrobenzenesulfonyl)-3-phenyl-azetidin-2-one.

55 NMR (CDCl₃): δ 8.3 (d, J=9, 2H), 8.2 (d, J=9, 2H), 7.2 (br.s., 5H), 4.0 (q, J=7, 2H), 3.7 (m, 2H), 1.2 (t, J=7, 3H). Similarly prepared was the corresponding *cis*-3-phenyl compound. NMR (CDCl₃): δ 8.4 (d, J=9, 2H), 8.25 (d, J=9, 2H), 7.2 (s, 5H), 5.0 (s, 1H), 3.7 (m, 3H), 0.85 (t, 5=7, 3H).

60 Following the same procedure as described above but using appropriate reagents, the following compounds were prepared:

(a) 4-Carboethoxy-1-(p-nitrobenzensulfonyl)-3-vinylazetidin-2-one

5 NMR (CDCl₃): *cis*: δ 8.3 (d, J=9, 2H), 8.2 (d, J=9, 2H), 5.2–6.0 (m, 3H), 4.0–4.6 (m, 4H), 1.2 (t, J=7, 3H); *trans*: δ 8.2 (d, J=9, 2H), 8.15 (d, J=9, 2H), 5.2–6.0 (m, 3H), 3.9–4.4 (m, 4H), 1.25 (t, J=7, 3H).

(b) 4-Carboethoxy-3-ethyl-1-(p-nitrobenzenesulfonyl)-azetidin-2-one

EXAMPLE 8

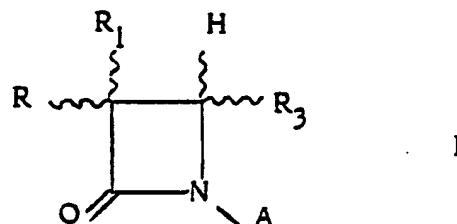
10 4-Acetoxy-3-n-propylazetidin-2-one-1-sulfonic acid tetrabutylammonium salt

15 A solution of 82 mg (0.463 mmole) 3-propyl-4-acethoxyazetidin-2-one in 5 ml pyridine was heated to 80°, 221 mg (1.39 mmole) sulfur trioxide-pyridine complex was added and the reaction mixture stirred at 80° one hour. It was then poured into 100 ml 0.5M KH₂PO₄ (aqueous) and washed with 2 × 25 ml CH₂Cl₂. The combined organic washes were backwashed with 25 ml 0.5M KH₂PO₄. 157 Mg (0.463 mmole) Bu₄NHSO₄ was added to the combined aqueous phases. This was extracted with 2 × 25 ml CH₂Cl₂ and the combined extracts were dried over MgSO₄, filtered, and stripped *in vacuo* to yield 12.4 mg of an oily residue which was chromatographed on a small silica gel column, eluted first with 75 ml hexane/ethyl acetate (3:1) to remove starting material, the with 100 ml ethyl acetate/methanol (4:1) to yield 13 mg (5.7%) 4-acethoxy-3-n-propylazetidin-2-one-1-sulfonic acid tetrabutylammonium salt.

20 NMR (CDCl₃): δ 1.0 (m, 16H), 1.75 (br m, 20H), 2.16 (s, 3H), 2.90 (br s, H), 3.1 (tr, 1H), 3.3 (tr, 8H), 4.08 (br tr, 1H), 6.18 (s, 1H).

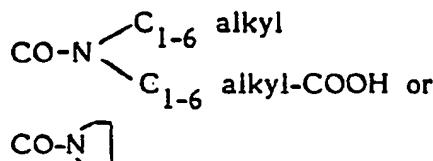
Claims

25 1. Compound of general formula I:



wherein:

- the wavy lines mean that R, R₁, H and R₃ can be at the α or the β positions and
 - R is: H or C_{1–6} alkyl.
 - R₁ is: H C_{1–6} alkyl C_{2–6} alkenyl C_{1–6} alkoxy or C₆H₅
 - R₃ is: SO–C_{1–6} alkyl COO–C_{1–6} alkyl COO–CH₂–C₆H₅ with C₆H₅ eventually substituted in para-position by –COOH O–CO–C_{1–6} alkyl with C_{1–6} alkyl eventually substituted in terminal position by –COOH O–CO–C₆H₅ O–C₆H₅ with C₆H₅ eventually substituted in para-position by –COOH



65 with the proviso that when A = H, if R = R₁ = H, R₃ is different of –O–CO–C_{1–6} alkyl, –O–CO–C₆–H₅ or O–C₆H₅ and if R = R₁ = CH₃, R₃ is different from O–CO–CH₃.

– A is: H CO–C_{1–6} alkyl, C_{1–6} alkyl eventually substituted by –COOH in terminal position

CO-C₆H₅
 CO-NH-C₁₋₆ alkyl
 CO-O-C₁₋₆ alkyl
 SO₃⁻(Bu)₄N⁺, or

5 SO₂-C₆H₅, C₆H₅ being substituted in para-position by NO₂ or CH₃.

2. Compound of general formula according to claim 1 selected between the following examples:

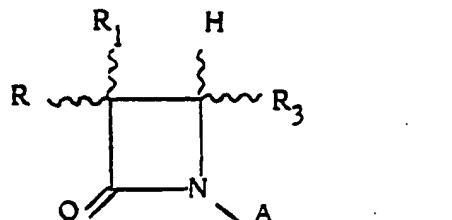
(a) 1-acetyl-4-methylsulfinylazetidin-2-one;
 (b) 1-acetyl-4-acetoxyazetidin-2-one;
 (c) 4-acetoxy-3-ethylazetidin-2-one;
 10 (d) 1-acetyl-4-acetoxy-3-ethylazetidin-2-one;
 (e) 1-acetyl-4-acetoxy-3-n-propylazetidin-2-one;
 (f) 3-phenyl-4-ethoxycarbonylazetidin-2-one;
 (g) 4-benzyloxycarbonyl-1-p-nitrophenylsulfonylazetidin-2-one;
 (h) 1-acetyl-4-acetoxy-3,3-dimethylazetidin-2-one;
 15 (i) 3-phenyl-4-ethoxycarbonyl-1-p-nitrophenyl-sulfonylazetidin-2-one;
 (j) 4-acetoxy-3-n-propylazetidin-2-one-1-sulfonic acid tetra(n-butyl)ammonium salt;
 (k) 4-ethoxycarbonyl-1-p-nitrophenylsulfonyl-3-vinylazetidin-2-one;
 (l) 4-ethoxycarbonyl-3-ethyl-1-p-nitrophenylsulfonylazetidin-2-one;
 (m) 4-ethoxycarbonyl-3-ethyl-1-p-methylphenylsulfonylazetidin-2-one;
 20 (n) 4-ethoxycarbonyl-3-n-propyl-1-p-nitrophenylsulfonylazetidin-2-one;
 (o) 3-allyl-4-ethoxycarbonyl-1-p-nitrophenylsulfonylazetidin-2-one.

3. Pharmaceutical composition for the prevention, control or treatment of inflammation and/or degeneration comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of formula I, according to one of claim 1 or 2.

25 4. For the manufacture of a medicament for the prevention, control or treatment of inflammation and/or degeneration, the use of a compound of formula I according to one of claim 1 or 2.

Patentansprüche

30 1. Verbindung der allgemeinen Formel I:



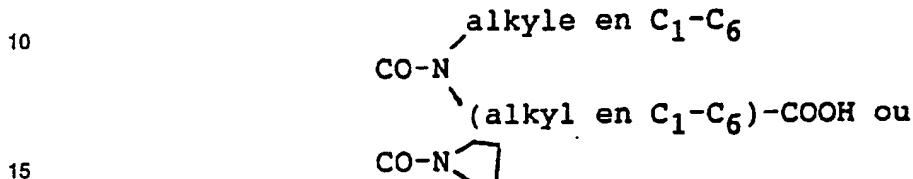
worin

- die geschwungenen Linien bedeuten, daß R, R₁, H und R₃ in der α- oder β-Stellung sein können und
- R H oder
- 45 C₁₋₆-Alkyl ist;
- R₁ H,
- C₁₋₆-Alkyl,
- C₂₋₆-Alkenyl,
- C₁₋₆-Alkoxy oder
- 50 C₆H₅ ist;
- R₃ SO-C₁₋₆-Alkyl,
- COO-C₁₋₆-Alkyl,
- COO-CH₂-C₆H₅, wobei C₆H₅ gegebenenfalls in der para-Stellung durch -COOH substituiert ist,
- O-CO-C₁₋₆-Alkyl, worin C₁₋₆-Alkyl gegebenenfalls in der Endstellung durch -COOH substituiert ist,
- 55 O-CO-C₆H₅,
- O-C₆H₅, wobei C₆H₅ gegebenenfalls in der para-Stellung durch -COOH substituiert ist,

60

65

– R_3 est un groupe SO-(alkyle en C₁–C₆),
COO-(alkyle en C₁–C₆),
COO-CH₂-C₆H₅, C₆H₅ étant éventuellement substitué en position para par –COOH,
O-CO-(alkyle en C₁–C₆), le groupe alkyle en C₁–C₆ étant éventuellement substitué en position terminale par –COOH,
O-CO-C₆H₅,
O-C₆H₅, C₆H₅ étant éventuellement substitué en position para par –COOH



à condition que, lorsque $A=H$, si $R=R_1=H$, R_3 soit différent de $-O-CO-(alkyle\ en\ C_1-C_6)$, $-O-CO-C_6H_5$ ou $O-C_6H_5$ et que, si $R=R_1=CH_3$, R_3 soit différent de $O-CO-CH_3$;

- A est H
- un groupe $CO-(alkyle\ en\ C_1-C_6)$, alkyle en C_1-C_6 éventuellement substitué par $-COOH$ en position terminale,
- $CO-C_6H_5$
- $CO-NH-(alkyle\ en\ C_1-C_6)$
- $CO-O-(alkyle\ en\ C_1-C_6)$
- $SO_3^-(Bu)_4N^+$, ou
- $SO_2-C_6H_5$, C_6H_5 étant substitué en position para par NO_2 ou CH_3 .

2. Composé de formule générale selon la revendication 1, choisi parmi les exemples suivants:

(a) 1-acétyl-4-méthylsulfinylazétidine-2-one;
(b) 1-acétyl-4-acétoxyazétidine-2-one;
(c) 4-acétoxy-3-éthylazétidine-2-one;
(d) 1-acétyl-4-acétoxy-3-éthylazétidine-2-one;
(e) 1-acétyl-4-acétoxy-3-n-propylazétidine-2-one;
(f) 3-phényl-4-éthoxycarbonylazétidine-2-one;
(g) 4-benzylxycarbonyl-1-p-nitrophénylsulfonylazétidine-2-one;
(h) 1-acétyl-4-acétoxy-3,3-diméthylazétidine-2-one;
(i) 3-phényl-4-éthoxycarbonyl-1-p-nitrophénylsulfonylazétidine-2-one;
(j) sel de tétra(*n*-butyl)ammonium de l'acide 4-acétoxy-3-n-propylazétidine-2-one-1-sulfonique;
(k) 4-éthoxycarbonyl-1-p-nitrophénylsulfonyl-3-vinylazétidine-2-one;
(l) 4-éthoxycarbonyl-3-éthyl-1-p-nitrophénylsulfonylazétidine-2-one;
(m) 4-éthoxycarbonyl-3-éthyl-1-p-méthylphénylsulfonylazétidine-2-one;
(n) 4-éthoxycarbonyl-3-n-propyl-1-p-nitrophénylsulfonylazétidine-2-one;
(o) 3-allyl-4-éthoxycarbonyl-1-p-nitrophénylsulfonylazétidine-2-one.

3. Composition pharmaceutique pour prévenir, enrayer ou traiter l'inflammation et/ou la dégénérescence, comprenant un véhicule pharmaceutique et une quantité thérapeutiquement efficace d'un composé de formule I, selon l'une des revendications 1 ou 2.

4. Pour la fabrication d'un médicament pour prévenir, enrayer ou traiter l'inflammation et/ou la dégénérescence, l'utilisation d'un composé de formule I selon l'une des revendications 1 ou 2.

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